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REVIEW ARTICLE

Efficacy of hypertonic saline versus mannitol in adult patients with severe head trauma: systematic review

Eficacia de la solución salina hipertónica frente al manitol en pacientes adultos con trauma craneoencefálico grave: revisión sistemática

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ABSTRACT

Severe traumatic brain injury (TBI) is the leading cause of disability and mortality worldwide, and hyperosmolar solutions have been used to treat it without a standardized choice. The efficacy of hypertonic saline solution (HSS) was compared with mannitol (MTL) in adult patients with severe or potentially severe moderate TBI, evaluating the decrease in intracranial pressure, level of consciousness, and serum osmolarity concentration to identify whether one is superior to the other. Nine articles that met the established inclusion and exclusion criteria were included, with a total of 979 participants and sample sizes ranging from 20 to 502; the bias of the articles was analyzed using scales. HHS is superior in terms of efficacy compared to LTM due to its sustained mechanism of action over time and lower recurrence of episodes of intracranial hypertension.

Keywords: traumatic brain injury, elevated intracranial pressure, hypertonic saline solution, mannitol, adult.

RESUMEN

El traumatismo craneoencefálico (TCE) grave es la principal causa de discapacidad y mortalidad a nivel mundial y para su manejo se han utilizado soluciones hiperosmolares sin una elección estandarizada. Se comparó la eficacia de la solución salina hipertónica (SHH) frente al manitol (MTL) en pacientes adultos con TCE grave o moderado potencialmente grave, evaluando la disminución de la presión intracraneal, nivel de conciencia y concentración de la osmolaridad sérica para identificar si existe superioridad de una sobre otra. Se incluyeron 9 artículos que cumplieron con los criterios de inclusión y exclusión establecidos con un total de 979 participantes con tamaños de muestra entre 20 a 502; el sesgo de los artículos fue analizado a través de escalas. La SHH presenta una superioridad en cuanto a su eficacia en comparación al MTL debido a su mecanismo de acción sostenido en el tiempo y menor recurrencia de episodios de hipertensión intracraneal.

Palabras clave: traumatismo craneoencefálico, hipertensión intracraneal, solución salina hipertónica, manitol, adulto.

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INTRODUCTION

Severe traumatic brain injury (TBI) is an injury that results from the exchange of kinetic energy at the level of the skull; the severity of the injury depends on the body's capacity to absorb the energy. It is classified according to severity as mild, moderate, and severe (Borja et al., 2021; Ginsburg & Smith, 2025). The kinetic event that triggers a TBI can cause brain tissue damage, known as the primary injury. Secondary injury is evident when there is neuronal damage due to cellular processes triggered by the primary injury. This damage appears hours or days after the traumatic event and can last for weeks (Moscote-Salazar et al., 2016; Kaur & Sharma, 2018). Changes in calcium homeostasis occur after the trauma; the intracellular flow of this ion is affected by the malfunction of membrane channels and receptors, resulting in disruption of the sodium-potassium pump. Likewise, traumatic brain injury (TBI) increases excitatory amino acids such as glutamate and aspartate, which bind to specific receptors like N-methyl-D-aspartate and AMPA-kainate. These receptors also activate sodium and calcium, leading to an inflammatory process (Moscote-Salazar et al., 2016).

TBI is considered the leading cause of disability and mortality worldwide, affecting approximately 759 people per 10,000 inhabitants (Diaz-Arrastia et al., 2024; Gordon & David, 2025). The most affected population is adolescents and young adults between the ages of 15 and 30; however, in the last 20 years, the incidence of TBI has doubled in the elderly population due to the risk of falls. For every three men affected, one woman is affected, in a ratio of 3:1. Traffic accidents are the leading cause of traumatic brain injury (TBI), followed by violent acts, falls, sports-related injuries, and penetrating trauma (Giner et al., 2022; Maleki et al., 2023; Williamson et al., 2023).

Currently, hyperosmolar solutions such as hypertonic saline (HSS) and mannitol (MTL) have been used for its management, with the latter being the most common. However, HSS has gained prominence, displacing mannitol as the first-line treatment for TBI. MTL is a diuretic that increases the osmolarity of tubular fluid, inhibiting the reabsorption of water and electrolytes. In the brain, it acts by establishing a gradient between plasma and parenchymal tissue, resulting in a reduction of brain water content (Chen et al., 2020). On the other hand, SHH has the capacity to mobilize fluids from brain tissue into the vascular space, reducing the water content in the brain parenchyma and, therefore, decreasing ICP (Gharizadeh et al., 2022).

It is important to analyze the efficacy of the aforementioned solutions, as currently no

clinical superiority of one over the other has been demonstrated; rather, the prevailing view is that their effectiveness is similar, since the most recent systematic reviews do not offer a clear picture of their differences, attributing this to a lack of sufficient evidence from comparative studies (Gharizadeh et al., 2022). However, most studies conclude that SHH may offer greater benefits. One consideration to keep in mind is that the latest systematic reviews include studies of both pediatric and adult patients, generalizing the treatment conclusions. Nevertheless, each population group should be analyzed individually, given that intracranial pressures differ in each group, and therefore, treatment and dosage also differ.

Given the imprecision in choosing a treatment for severe TBI during an emergency, the objective of this research is to compare the efficacy of hypertonic saline solution (HSS) versus mannitol (MTL) in severe TBI in adult patients, to contribute to medical practice by supporting better decision-making based on solid findings, evaluating the reduction of intracranial pressure, level of consciousness, and serum osmolarity concentration through the extraction, comparison, and synthesis of updated scientific evidence.

METHODOLOGY

A systematic review was conducted following the PRISMA international guidelines. Randomized controlled trials, prospective case-control studies, and prospective and retrospective cohort studies were included; these were published in databases such as PubMed, Scopus, Cochrane, Taylor & Francis, Medline, Springer Nature, and ScienceDirect. The same search was also performed in registries such as ClinicalTrials and CenterWatch. Search terms and Boolean operators such as “traumatic brain injury” AND “mannitol” AND “hypertonic saline” NOT “children” were used to collect articles. The search was conducted from March to July 2025. Study selection was based on the following criteria: studies that included adult patients diagnosed with severe or moderately severe traumatic brain injury (TBI), that compared the simultaneous administration of hypertonic saline and mannitol, that evaluated intracranial pressure (ICP) control, that were published in English or Spanish, and that had been published within the last 5 years. However, studies with dates outside this range were considered due to the relevance of their information. Studies were excluded if they met any of the following criteria: patients diagnosed with other types of traumas, clinical trials conducted on animals, studies with small sample sizes, or studies with significant limitations as described in the corresponding section.

The researchers manually assessed all studies. Eligibility was determined by analyzing the following: study title, year of publication, objectives, methodology, study design, population, sample size, allocation, randomization, blinding, primary outcomes, and conclusions. Duplicate removal was performed using the Rayyan application by manually uploading the articles. Data extraction was performed using a Microsoft Excel spreadsheet that included the following sections: author name and year of publication, number of participants, intervention, and primary and secondary outcomes. The specific outcomes analyzed were the reduction in intracranial pressure (ICP), level of consciousness, and serum osmolality concentration, measured at all time points. Other variables analyzed included mortality, cytoprotection, and percutaneous coronary intervention (PCI). To assess the methodological quality of the studies, the GRADE scale was used. An independent evaluation of the included articles was also performed using the JADAD scale (Manterola & Otzen, 2015) for clinical trials and the Newcastle-Ottawa (NOS) scale (Wells et al., 2000) for observational studies. Potential biases that could have influenced the interpretation of results were analyzed using the Cochrane ROBvis tool (McGuinness & Higgins, 2021). For randomized controlled trials (RCTs), RoB 2.0 was used, and for observational studies, ROBINS 1 was used, analyzing the reduction in intracranial pressure (ICP), considered the most significant variable. Furthermore, to avoid publication bias, trial protocols with and without published results were analyzed.

RESULTS AND DISCUSSION

The selection of relevant articles was performed using the PRISMA flowchart (Figure 1). In summary, of the 1397 results from the database search, 9 studies were included in this systematic review (Vialet et al., 2003; Sakellaridis et al., 2011; Hendoui et al., 2013; Jagannatha et al., 2016; Patil & Gupta, 2019; Huang et al., 2020; Mangat et al., 2020; Tatro et al., 2020; Van Veen et al., 2023). Three were analytical observational studies, and the remaining 6 were randomized controlled trials. Publication years ranged from 2003 to 2023, and sample sizes ranged from 20 to 502 participants (Table 1).

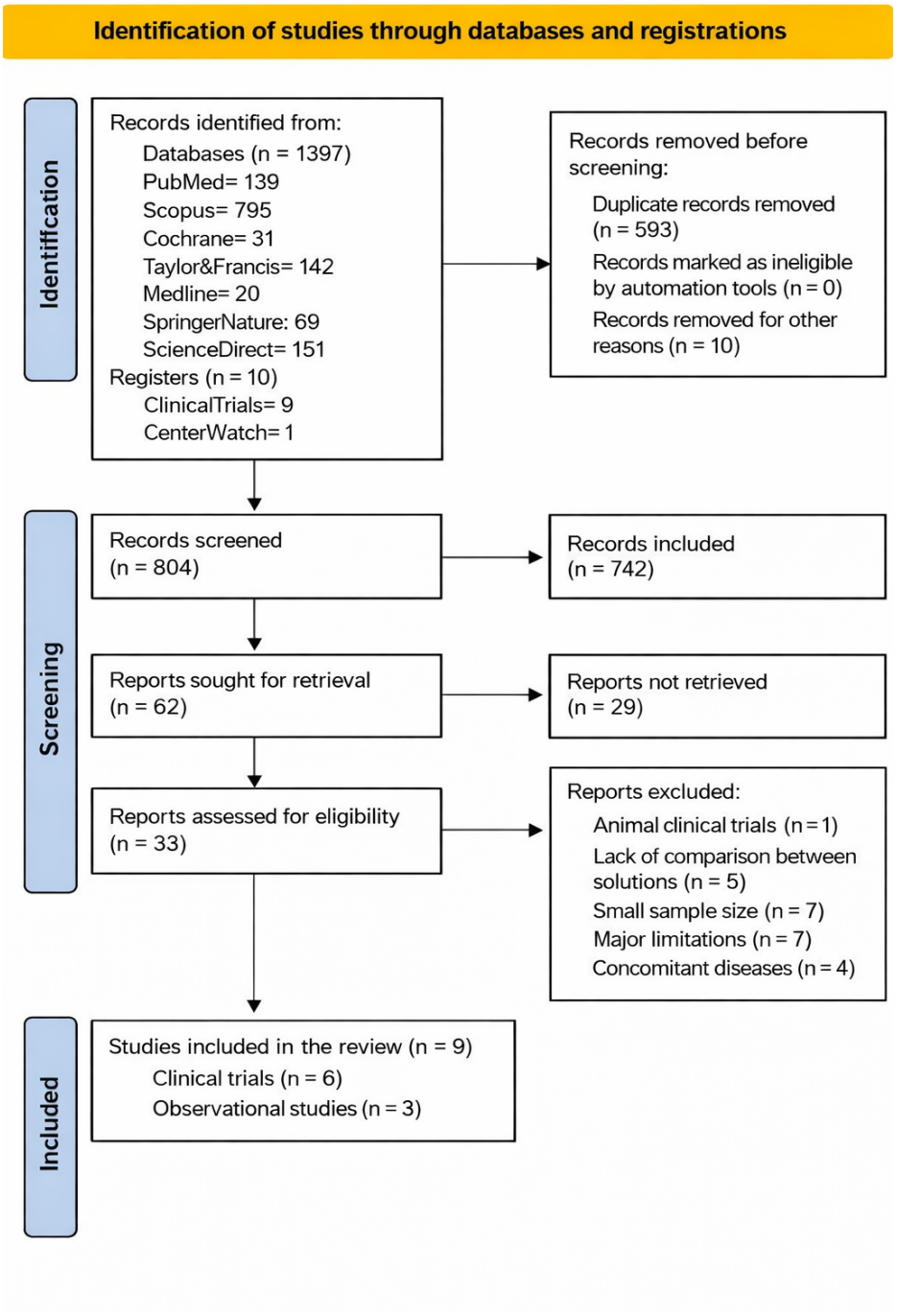
Identification of studies through databases and registrations
Identification
Records identified from:
Databases (n = 1397)
PubMed= 139
Scopus= 795
Cochrane= 31
Taylor&Francis= 142
Medline= 20
SpringerNature: 69
ScienceDirect= 151
Registers (n = 10)
ClinicalTrials= 9
CenterWatch= 1
Records removed before screening:
Duplicate records removed (n = 593)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 10)
Screening
Records screened (n = 804)
Records included (n = 742)
Reports sought for retrieval (n = 62)
Reports not retrieved (n = 29)
Reports assessed for eligibility (n = 33)
Reports excluded:
Animal clinical trials (n = 1)
Lack of comparison between solutions (n = 5)
Small sample size (n = 7)
Major limitations (n = 7)
Concomitant diseases (n = 4)
Included
Studies included in the review (n = 9)
Clinical trials (n = 6)
Observational studies (n = 3)

Figure 1. PRISMA flowchart.

Table 1. Individual results of selected articles

Reference	Number of participants	Intervention	Result primary	Result secondary
Patil & Gupta (2019)	Patients >18 years, with ECG ≤8 and with severe TBI. N = 120	3 groups of 40 assigned with SSH at 3%, MTL 20%, and 10% MTL plus glycerol.	SSH at 3% achieved a greater initial reduction in less time at 10 minutes of infusion compared to MTL at 20% and MTL at 10% plus glycerol (p=0.0245).	Osmolarity increased with all solutions (p < 0.0001), as did the ECG (p < 0.0001). The greatest osmotic impact was with the SSH bolus, and the highest ECG value was observed in the SSH group.
Mangat et al. (2020)	Patients with TBI from the TBI-trac study. N = 123	A 1:1 ratio with 25 patients for each solution and another 1:2 ratio with 25 patients with SSH (24 at 3% and 1 at 23.4%) and 48 with MTL at 20%.	After monitoring for 6 to 7 days, ICP control was achieved faster with SSH than with MTL (p <0.01). This was analyzed with the equation (low CPP + high ICP), improving in 11 hours with SSH, while with mannitol it took 30 hours	-
Van Veen et al. (2023)	Patients ≥16 years with TBI in ICU. N= 502.	First group with SHH at 3% (n=287), the second with MTL at 20% (n=149), and the third with both solutions (n=66).	ICP did not decrease significantly with the combined treatment, compared to those treated only with SHH and MTL (p= 0.001).	-
Huang et al. (2020)	Patients >18 years, with severe TBI and with GCS ≤ 8.N = 83.	MTL at 20% or SSH at 10% alternated in each HIC event.	The reduction in ICP was similar between SSH (9.8±3.1 mmHg) and MTL (8.9±2.6 mmHg) (p>0.05).	Osmolality was maintained for a longer time with SSH than with MTL (p < 0.05). The GOS categorized 36 patients as favorable, 34 moderate, 7 serious, 9 vegetative, and 7 deceased.
Hendoui et al. (2013)	Adults with severe TBI, GCS ≤ 12, and edema on CT scan. N = 33	Group A (n=10) with 20% MTL, group B (n=11) with 5% SSH, and group C (n=12) with 5% SSH in continuous infusion.	-	Bolus SSH had a greater increase in osmolarity than MTL (p = 0.01). ECG increased significantly with all solutions (p=0.10).
Vialet et al. (2003)	Patients >18 years with severe TBI, with GCS ≤8. N = 20	Groups of 10 patients were randomly assigned to SSH 7.5% or 20% MTL.	SSH resulted in fewer ICH episodes per day compared to MTL (p = 0.02). The total daily duration of ICH episodes was shorter in the SSH group (p = 0.04).	After 4 hours of osmotic therapy, serum osmolarity was higher in the SSH group (p = 0.01).

Reference	Number of participants	Intervention	Result primary	Result secondary
			Treatment failure was lower with SSH (1 of 10 patients) than with mannitol (7 of 10 patients) (p = 0.01).	
Jagannatha et al. (2016)	Adult patients with severe TBI, with a GCS ≤ 8. N = 38	18 patients in the SSH 3% group and 20 in the MTL 20% group.	An R^2 analysis comparing baseline ICP versus magnitude of ICP reduction after MTL and SSH administration was R^2 = 0.2369 vs 0.5749, respectively (p= 0.0001).	Patients presented similar levels of consciousness at ICU discharge and when they were discharged from the hospital (p= 0.98). Osmolarity shows no significant difference between SSH and MTL (290 ± 6 vs. 297 ± 22) (p=0.71).
Sakellaridis et al. (2011)	Patients who presented with severe TBI (GCS ≤8). N=29	The administration was randomized and crossover.	SSH achieved a decrease in PIC with an average of 8.43 mmHg, while MTL had an average of 7.96 mmHg (p=0.586).	At 3 months, the GOS categorized the patients as follows: 7 dead, 1 vegetative, 2 in poor condition, 8 in moderate condition, and 11 in good condition.
Tatro et al. (2020)	Patients with TBI >16 years, who presented with an ICP ≥20. N=31	13 patients received only SSH, 4 received only MTL, and 14 received both agents.	No difference was found statistically significant for absolute reduction of ICP at 30, 60, and 120 minutes (p = 0.7456).	-

ICP: intracranial pressure, HSS: hypertonic saline solution, MTL: mannitol, TBI: traumatic brain injury, ICH: intracranial hypertension, GCS: Glasgow Coma Scale, mmHg: millimeters of mercury, IV: intravenous, ICU: intensive care unit, EVD: external ventricular drainage, R^2: coefficient of determination. CT: computed tomography, GOS: qualitative Glasgow Outcome Scale, N/n: number of patients treated, CPP: cerebral perfusion pressure, p: probability of outcome.

Using the JADAD scale, 83% of the studies were of high quality and 17% of low quality. Similarly, using the NOS scale, 100% of the articles were of high quality. Finally, the methodological quality of the systematic review, assessed using the GRADE scale, resulted in 55.55% high quality and 44.44% moderate quality, with an overall average of 3.56, indicating high methodological quality. With RoB 2.0 (Figure 2), 100% were at low risk of bias, and with ROBINS I (Figure 3), 66.6% were at low risk and 33.3% at moderate risk. According to the assessment, the most frequent bias in the RCTs was the lack of explanation of blinding.

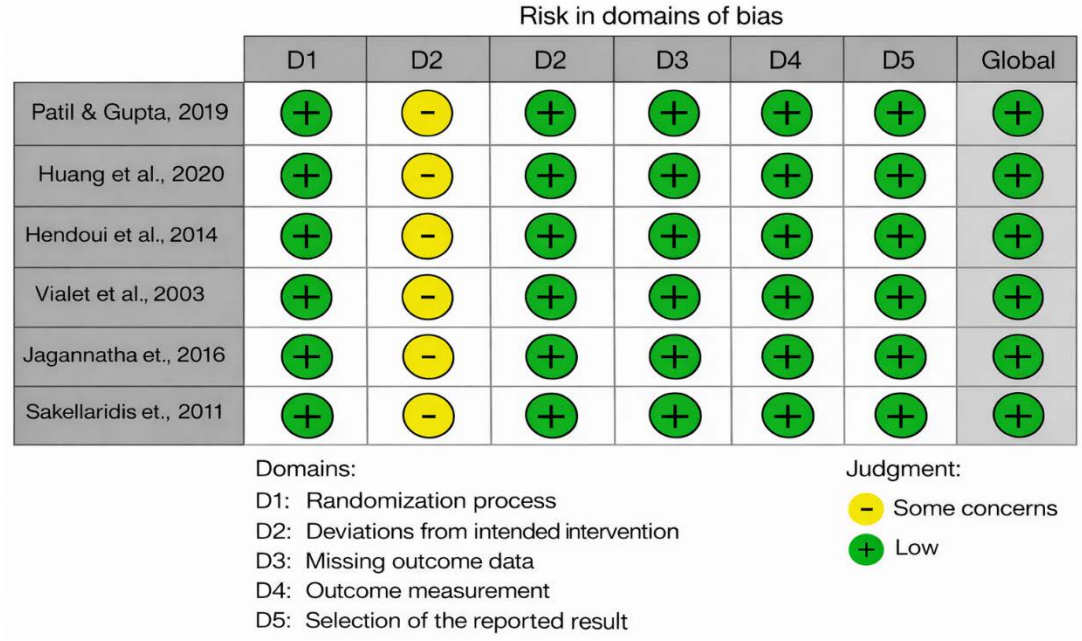

Figure 2. Rob 2.0 risk of bias summary.

A total of 9 articles were included, encompassing 979 adult patients with severe or moderately severe traumatic brain injury (TBI) without any other type of trauma. Patil & Gupta (2019) identified that hypertonic saline (HS) achieved an initial reduction in intracranial pressure (ICP) in a shorter time. Similarly, Vialet et al. (2003) and Mangat et al. (2020) reported that a greater reduction in ICP, fewer hypertensive episodes, and a lower rate of treatment failure were observed after 6 and 7 days of treatment following HSP administration.

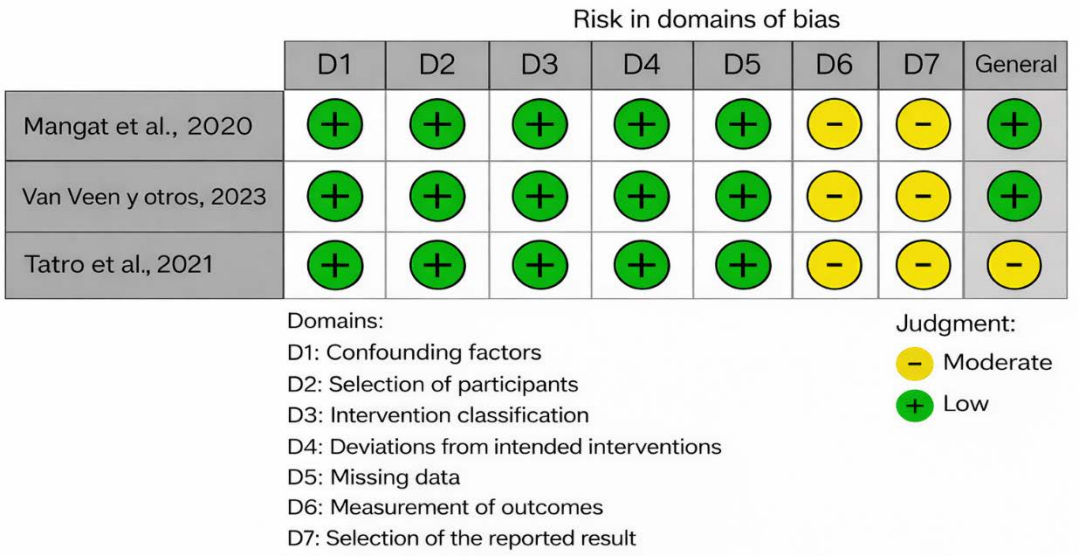

Figure 3. ROBINS I risk of bias summary.

Furthermore, Jagannatha et al. (2016) described in their study that the higher the ICP at the start of treatment, the more effective HSP is at reducing it. Finally, four studies (Sakellaridis et al., 2011; Huang et al., 2020; Tatro et al., 2020; Van Veen et al., 2023), including three clinical trials and one observational study, identified similar efficacy between hypertonic saline (HSS) and methyl laxatives (MLT) in patients with sustained intracranial pressure (ICP).

Regarding serum osmolarity, Hendoui et al. (2013) and Huang et al. (2020) found that after HSS administration, this parameter increased quantitatively and remained elevated for a longer period, while other studies found that measured serum osmolarity values were similar when administering either hyperosmolar solution (Vialet et al., 2003; Jagannatha et al., 2016; Patil & Gupta, 2019). Regarding the level of consciousness, at six months post-event, Huang et al. (2020) reported a favorable and moderate level on the Glasgow Outcome Scale (GOS) in 84.3% of patients, while in the study by Sakellaridis et al. (2011), this value was 65.5% at 3 months post-treatment. Furthermore, Patil & Gupta (2019) observed that the level of consciousness reached its maximum value after the administration of hypertonic saline (HSS); however, according to Hendoui et al. (2013) and Jagannatha et al. (2016), the level of consciousness is independent of the solution administered.

The present systematic review analyzed the efficacy of HSS versus methyl laxative (ML) in adult patients with severe traumatic brain injury (TBI). In 5 of the included studies, hypertonic

saline solution (HSS) achieved greater efficacy in the treatment of severe traumatic brain injury (TBI), either by demonstrating a greater sustained reduction in intracranial pressure (ICP), avoiding recurrences of intracranial hypertension (ICH), a lower rate of therapeutic failure, or showing better results by improving the level of consciousness; suggesting that HSS has a possible clinical advantage in contexts where rapid and sustained ICP control is critical. These results are consistent with other studies (Gu et al., 2019; Shi et al., 2020; Schwimmbeck et al., 2021; Cai & He, 2024; Karamian et al., 2024) that mention a greater sustained effect on ICP, effectively increasing CPP, preventing rebound edema, and presenting fewer associated adverse effects. Furthermore, it can be used in patients with comorbidities such as liver failure (Egea et al., 2020; Kareemi et al., 2023; Park et al., 2024). Regarding mortality, Jagannatha et al. (2016) and Van Veen et al. (2023) report that it was similar regardless of the solution, although not statistically significant at 6 months. This finding is supported by a recent meta-analysis by Miyoshi et al. (2020), which reaches the same conclusion; on the other hand, Patil & Gupta (2019) found that after SSH administration, the GOS reached its maximum value. Hendoui et al. (2013) further state that SHH also offers cytoprotection, giving it an advantage over MTL. This is reinforced by another article (Egea et al., 2020), which mentions that it even achieves cell preservation in systems other than the nervous system.

In the articles that support the idea of the superiority of SHH over MTL, there is a low risk of bias in the primary variable, strengthening the quality of their results and, therefore, their conclusions. However, studies with more representative populations report a similarity between both solutions. The superiority of SHH at a physiological level can be explained because, unlike other osmotic agents with a diuretic effect such as MTL, SHH favors the expansion of intravascular volume without causing a significant loss of fluids, allowing for adequate hemodynamic support, increasing both mean arterial pressure and cerebral blood flow, which favors the oxygenation of compromised brain areas (Guyton & Hall, 2016; Loscalzo et al., 2023; Smith & Spideh, 2024).

Although 55.5% of the articles reported that SSH was more effective than MTL, 44.4% stated that there were no significant differences in efficacy (DeNett & Feltner, 2019; Iqbal et al., 2023; Bernhardt et al., 2024; Karamian et al., 2024). The risk of bias was low in three of the articles supporting this idea, and moderate in Tatro et al. (2020). However, in the studies by Mangat et al. (2020) and Van Veen et al. (2023), despite their final risk of bias result being low, they presented some inconsistencies in the interventions applied, which would reduce their internal validity.

Furthermore, most of these articles are observational analytical studies, which are at a lower level than the clinical trials that support the superiority of SSH. Despite this, an important point to consider is that one of the four articles mentioned (Van Veen et al., 2023) has the largest sample size analyzed; therefore, its internal validity is likely to increase, supporting the lack of superiority of one solution over another.

One of the main strengths of this review is the pathophysiological explanation of the superiority of SSH over MTL, in addition to the inclusion of articles that only analyzed adult patients, since most of the reviews published to date mix articles from adult and pediatric populations, without taking into account that the management is different due to its physiological mechanisms and the doses. However, one of the most significant limitations is that the included articles did not only analyze HSS and MTL but also included combinations of both solutions or a third drug with different combinations. Furthermore, the concentrations of HSS were not the same in all studies, which limits the generalizability of the results. The age at which patients are considered adults varies depending on the researcher's criteria within the articles. Limitations during the review included language restrictions, as only studies in English and Spanish were selected, which could have introduced publication bias based on language. Although registries were analyzed, these were not included due to a lack of results, representing a methodological limitation.

Therefore, more clinical trials with larger, multicenter populations are needed, using the same concentration of HSS and without combining solutions. Furthermore, the blinding used, if employed, should be specified and detailed, and these interventions should be specifically applied to adult populations over 18 years of age.

CONCLUSIONS

Based on the available evidence, hypertonic saline solution was determined to be more effective than mannitol in the management of severe traumatic brain injury in adult patients. This is due to its sustained action and lower recurrence of intracranial hypertension episodes, resulting in less therapeutic failure. However, these results cannot be fully extrapolated for generalization because the study population consisted of only 333 individuals, and those studies with a representative population used crossover treatments. Furthermore, several articles used hypertonic solutions with varying concentration percentages, which could influence the final results by

altering the time, speed, or intensity of the therapeutic effect. Therefore, to generalize these results, further research in larger sample sizes is recommended.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Alexander Expósito and Amelie N. Silva. **Data curation:** Nicolle M. Capelo. **Formal analysis:** Alexander Expósito. **Investigation:** Alexander Expósito, Amelie N. Silva, Nicolle M. Capelo, Carlos F. Zamora, and Doris G. Cuji. **Methodology:** Alexander Expósito, Amelie N. Silva, Nicolle M. Capelo, Carlos F. Zamora, and Doris G. Cuji. **Project administration:** Alexander Expósito and Amelie N. Silva. **Resources:** Alexander Expósito and Amelie N. Silva. **Software:** Amelie N. Silva, Nicolle M. Capelo, Carlos F. Zamora, and Doris G. Cuji. **Supervision:** Alexander Expósito and Amelie N. Silva. **Validation:** Alexander Expósito. **Visualization:** Amelie N. Silva and Carlos F. Zamora. **Writing – original draft:** Nicolle M. Capelo and Doris G. Cuji. **Writing – review & editing:** Alexander Expósito, Amelie N. Silva, Nicolle M. Capelo, and Doris G. Cuji.

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